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Behçet's disease and pulmonary involvement

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ABSTRACT

Behçet's disease (BD) is a systemic vasculitis involving arteries and veins of all sizes and is characterized by a heterogeneous spectrum of clinical manifestations, including mucocutaneous, ocular, vascular, and neurological involvement, typically following a relapsing-remitting course. Although thoracic involvement is infrequent, it can affect various anatomical structures within the chest and present with a wide range of clinical symptoms. Pulmonary artery involvement may lead to life-threatening complications such as pulmonary artery aneurysms (PAAs) and pulmonary artery thrombosis (PAT), which are significant causes of mortality in BD. Timeyl diagnosis, appropriate radiological assessment, prompt initiation of immunosuppressive therapy are critical to reducing morbidity and mortality. This review provides an overview of the pulmonary manifestations of BD.

Keywords: Vasculitis, Behçet's disease, pulmonary artery aneurysm, pulmonary artery thrombosis

INTRODUCTION

Behçet's disease (BD) is a chronic multisystemic vasculitis of unknown etiology. It was first described in 1937 by Hulusi Behçet in three patients with oral and genital ulcerations, uveitis, and erythema nodosum.[1,2] BD is an autoinflammatory vasculitis that can affect arteries and veins of all sizes, with the most common characteristic findings including venular involvement and pulmonary artery aneurysms (PAAs). Although BD is a form of vasculitis, the vasculitis lesions in BD lack necrotizing vasculitis or giant cell formation. Autoantibodies are not positive. Leukocytoclastic vasculitis and fibrinoid necrosis of the vessel wall are observed.[2]

Although its etiology remains unclear, environmental factors are considered to trigger BD in individuals with a genetic predisposition. BD is not genetically transmitted through Mendelian inheritance, while its high incidence along the Silk Road implicates the role of genetic factors in the development of the disease. The disease has been found to be more prevalent in carriers of HLA-B51/HLAB5. HLA B51 is a common genetic factor in Japanese, Middle Eastern, and Turkish populations.[3] In a review evaluating studies from 12 countries in Latin America, HLA-B51 positivity was found to be 38% in Argentina, 30% in Brazil, and 9% in Mexico.[4] Several factors including tumor necrosis factor (TNF), heat shock proteins, and major histocompatibility complex class I have been identified in the etiology. Genetic differences in MHC-1 opathies are controversial. Mitochondrial DNA is considered to play a role in the new inflammatory pathway.[2,5] Epidemiologically, BD has been identified in both sexes between the ages of 20 and 40. It is more severe in young populations and in males. Geographical differences in incidence between males and females and in terms of organ involvement have been reported.[2]

Clinical symptoms of BD are often heterogeneous and there are no pathognomonic laboratory findings. Diagnosis is made based on clinical criteria as well as international diagnostic criteria. The disease has been shown to be characterized by a decrease in the number of attacks and remissions with advanced age.[6,8] As a systemic vasculitis, it commonly manifests with mucocutaneous lesions and may also present with musculoskeletal, vascular, ocular, neurological, and gastrointestinal involvement.[2,6] Venous involvement is far more common than arterial involvement. Most common pulmonary manifestation is PAA or pulmonary artery thrombosis (PAT). Pulmonary involvement was commonly reported in studies published in the 1960s. Varying incidence rates ranging from 1% to 10-16% have been reported. Generally, screening for pulmonary involvement is not preferred unless clinical findings are suggestive.[9,10] The aim of this review was to summarize pulmonary involvement in BD in light of current literature.

PULMONARY INVOLVEMENT

In BD, elevated levels of free oxygen radicals have been observed, resulting from neutrophile hyperfunction. In turn, increased release of free oxygen radicals from neutrophils can cause acute inflammatory tissue damage, leading to superoxide-mediated injury in the respiratory pathways,

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which subsequently contributes to pulmonary involvement.[8] It has been reported that pulmonary involvement occurs within 3 to 4 years after diagnosis.[11]

Clinical manifestations vary depending on immunological variations.[8] Most common clinical findings reported in studies include dyspnea, cough, chest pain, pleural pain, fever, excessive sweating, and hemoptysis. Nonspecific bronchial hyperreactivity is also observed due to increased inflammation.[8,11]

Radiographic examination with posterior anterior chest radiography or computed tomography (CT) often presents with aneurysms of the thoracic aorta, pulmonary artery, or mediastinal veins with hilar and mediastinal widening, and rarely, nonspecific focal opacities due to parenchymal involvement.[10] Studies have reported that chest radiography is normal in 31.2% of cases of isolated PAT and other involvement. CT is recommended for patients with suspected pulmonary involvement. Cavitary lesions, subpleural nodules, and consolidations can be detected on CT. Common acute phase symptoms include subpleural nodules and infarctions in the presence of hemoptysis, while cavitation is the hallmark symptom in the chronic phase. This is due to the infarction and necrosis in the nodules.[8] Arterial and venous manifestations are mainstay features of BD, both of which are valuable in the differential diagnosis of other forms of vasculitis.[8] Ultrasonography (USG) is recommended for imaging venous and arterial systems, which is particularly used to demonstrate inflammation and thrombosis in venous vessels. Magnetic resonance angiography (MRA) is an alternative imaging modality for assessing the venous vessel wall.[12]

There are two main pulmonary artery manifestations in BD: PAA and PAT. It has been shown that the right ventricle is involved in 30% and deep vein thrombosis (DVT) occurs in 80% of BD patients. DVT can be present in both the lower and upper extremities and is a finding detected in pulmonary embolism. Vascular involvement has been shown to be more common in males approximately within the one-year period after disease onset. In one-third of those affected, venous involvement manifests as superior vena cava syndrome, pulmonary thromboembolism, or cerebral venous thrombosis.[13,14] Aneurysms are frequently observed in the main pulmonary artery and its branches.[13] BD is a cause of mortality and morbidity, with a reported mortality rate of 26%.[15] Although Hughes-Stovin syndrome, particularly in PAAs, resembles BD both radiologically and histopathologically, it lacks the characteristic oral and genital ulcerations seen in BD. Bronchiectasis resulting from vascular compression by PAAs has been identified in BD.[8,10] Aneurysms have been reported as saccular-or fusiform-shaped. They may contain partial thrombus. In PAT, occlusion, stenosis, and mural thrombus are observed in the vascular lumen. Studies on aneurysms and thrombus have found that they are more common bilaterally and in the inferior lobe artery. Recurrence rate after treatment has been reported as 40%.[8,14,17]

The incidence of parenchymal and pleural involvement has been reported as 1-10%. Pulmonary infarction, atelectasis, and hemorrhage occur secondary to pulmonary artery occlusion or PAT. Focal and subpleural consolidation on CT are signs of pulmonary infarction. Nodules can be detected in diffuse airways obstruction caused by hemorrhage. Small vessel disease, bronchitis, fibrosis, emphysema, eosinophilic pneumonia, and cryptogenic organizing pneumonia are other types of manifestations. Parenchymal involvement is nonspecific.[10,17,18] Cases of multiple parenchymal cystic lesions, parenchymal infarctions, and air trapping due to peribronchial cuffing, stenosis, or occlusion have been reported.[8,19] Case reports have documented multiple parenchymal cystic lesions attributed to air trapping secondary to parenchymal infarctions or stenosis/occlusion resulting from peribronchial inflammation.

Mediastinal involvement can be seen in the diffuse form of fibrosing mediastinitis and collateral obstruction of superior vena cava.[10]

TREATMENT

The primary goal is to suppress inflammation, with the ultimate aim of reducing relapses and damage in major organ involvement. A multidisciplinary approach is essential in induction and maintenance therapy.[12]

Corticosteroids, cyclophosphamide, azathioprine, and cyclosporine are recommended for immunosuppressive therapy. The choice of these medications varies depending on age, gender, organ type involved, disease severity, and disease duration. Initial treatment with pulse corticosteroids is recommended for severe pulmonary involvement. The use of anticoagulants in vascular manifestations is controversial. Anti-TNF-alpha (anti-TNFα) is recommended for recurrent thrombosis. One of the leading problems in these cases is post-thrombotic syndrome. High-dose corticosteroids and cyclophosphamide are recommended for both PAA and PAT. Azathioprine may be considered as an alternative. There are also case reports documenting the use of cyclophosphamide and infliximab in relapses and recurrences. Alternatively, tocilizumab is recommended for vascular involvement. In some cases, endovascular treatment may be required for PAAs.[12,15,20-23]

ETHICAL DECLARATIONS

Referee Evaluation Process

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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